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NOVEL BENZOTHIEPINES HAVING ACTIVITY AS INHIBITORS OF ILEAL BILE ACID TRANSPORT AND TAUROCHOLATE UPTAKE

This application is a continuation-in-part application of U.S. Application Serial No. 09/816,065, filed March 11, 1997, which claims the benefit of priority of U.S. Provisional Application Serial No. 60/013,119, filed March 11, 1996. This application is also a continuation-in-part application of U.S. Application Serial No. 09/831,284, filed March 31, 1997, which is a continuation of U.S. Application Serial No. 08/517,051, filed August 21, 1995, which is a continuation-in-part application of U.S. Application Serial No. 08/305,526, filed September 12, 1994. This application also claims priority from U.S. Provisional Application Serial No. 60/068,170 filed December 19, 1997.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to novel benzothiepines, derivatives and analogs thereof, pharmaceutical compositions containing them, and their use in medicine, particularly in the prophylaxis and treatment of hyperlipidemic conditions such as is associated with atherosclerosis or hypercholesterolemia, in mammals.

Description of Related Art

It is well-settled that hyperlipidemic conditions associated with elevated concentrations of total cholesterol and low-density lipoprotein cholesterol are major risk factors for coronary heart disease and particularly atherosclerosis. Interfering with the

circulation of bile acids within the lumen of the intestinal tract is found to reduce the levels of serum cholesterol in a causal relationship. Epidemiological data has accumulated which indicates such reduction leads to an improvement in the disease state of atherosclerosis. Stedronsky, in "Interaction of bile acids and cholesterol with nonsystemic agents having hypocholesterolemic properties," Biochimica et Biophysica Acta, 1210 (1994) 255-287 discusses the biochemistry, physiology and known active agents surrounding bile acids and cholesterol.

Pathophysiologic alterations are shown to be consistent with interruption of the enterohepatic circulation of bile acids in humans by Heubi, J.E., et al. See "Primary Bile Acid Malabsorption: Defective in Vitro Ileal Active Bile Acid Transport", Gastroenterology, 1982:83:804-11.

In fact, cholestyramine binds the bile acids in the intestinal tract, thereby interfering with their normal enterohepatic circulation (Reihnér, E. et al, in "Regulation of hepatic cholesterol metabolism in humans: stimulatory effects of cholestyramine on HMG-CoA reductase activity and low density lipoprotein receptor expression in gallstone patients", Journal of Lipid Research, Volume 31, 1990, 2219-2226 and Suckling el al, "Cholesterol Lowering and bile acid excretion in the hamster with cholestyramine treatment", Atherosclerosis, 89(1991) 183-190). This results in an increase in liver bile acid synthesis by the liver using cholesterol as well as an upregulation of the liver LDL receptors which enhances clearance of cholesterol and decreases serum LDL cholesterol levels.

In another approach to the reduction of recirculation of bile acids, the ileal bile acid transport system is a putative pharmaceutical target

for the treatment of hypercholesterolemia based on an interruption of the enterohepatic circulation with specific transport inhibitors (Kramer, et al, "Intestinal Bile Acid Absorption" The Journal of Biological Chemistry, Vol. 268, No. 24, Issue of August 25, pp. 18035-18046, 1993).

In a series of patent applications, eg Canadian Patent Application Nos. 2,025,294; 2,078,588; 2,085,782; and 2,085,830; and EP Application Nos. 0 379 161; 0 549 967; 0 559 064; and 0 563 731, Hoechst Aktiengesellschaft discloses polymers of various naturally occurring constituents of the enterohepatic circulation system and their derivatives, including bile acid, which inhibit the physiological bile acid transport with the goal of reducing the LDL cholesterol level sufficiently to be effective as pharmaceuticals and, in particular for use as hypocholesterolemic agents.

In vitro bile acid transportinhibition is disclosed to show hypolipidemic activity in The Wellcome Foundation Limited disclosure of the world patent application number WO 93/16055 for "Hypolipidemic Benzothiazepine Compounds"

Selected benzothiepines are disclosed in world patent application number WO93/321146 for numerous uses including fatty acid metabolism and coronary vascular diseases.

Other selected benzothiepines are known for use as hypolipaemic and hypocholesterolaemic agents, especially for the treatment or prevention of atherosclerosis as disclosed by application Nos. EP 508425, FR 2661676, and WO 92/18462, each of which is limited by an amide bonded to the carbon adjacent the phenyl ring of the fused bicyclo benzothiepine ring.

The above references show continuing efforts to

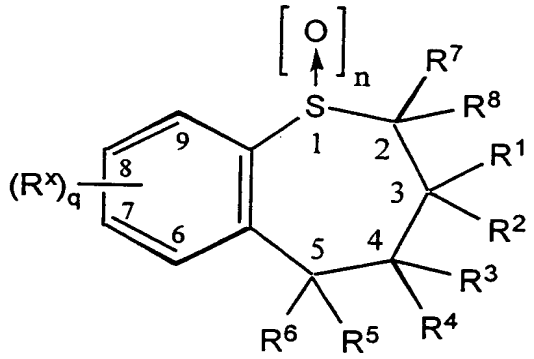
find safe, effective agents for the prophylaxis and treatment of hyperlipidemic diseases and their usefulness as hypocholesterolemic agents.

Additionally selected benzothiepines are disclosed for use in various disease states not within the present invention utility. These are EP 568 898A as abstracted by Derwent Abstract No. 93-351589; WO 89/1477/A as abstracted in Derwent Abstract No. 89-370688; U.S. 3,520,891 abstracted in Derwent 50701R-B; US 3,287,370, US 3,389,144; US 3,694,446 abstracted in Derwent Abstr. No. 65860T-B and WO 92/18462.

The present invention furthers such efforts by providing novel benzothiepines, pharmaceutical compositions, and methods of use therefor.

SUMMARY OF THE INVENTION

Accordingly, among its various apects, the present invention provides compounds of formula (I):



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wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl,

dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{10}R^wA^-$, SR^9, $S^+R^9R^{10}A^-$. $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A-$, S, SO, SO_2, $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9, R^{10}, and R^w are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3-C_{10} cycloalkyl;

R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9, wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form =O, $=NOR^{11}$, =S, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2, and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

R^5 and R^6 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^9, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13}, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein:

A^- is a pharmaceutically acceptable anion and M is a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13}, R^{14}, and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13}, R^{14}, and R^{15} are optionally substituted with

one or more groups selected from the group consisting of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, guanidinyl, OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A-$, $S^+R^9R^{10}A-$, and $C(O)OM$,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

R^{13} and R^{14}, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R^{14} and R^{15}, together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13}, $S^+R^{13}R^{14}A-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)OM$, COR^{13}, OR^{18}, $S(O)_nNR^{18}$, $NR^{13}R^{18}$, $NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid,

peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or C(O)OM, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_3R^9, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and C(O)OM,

wherein in R^x, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, $P(O)R^{13}$, $P^+R^{13}R^{14}A-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, S^+R^9A-, PR^9, $P^+R^9R^{10}A-$, or $P(O)R^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more groups selected from the group consisting of alkyl,

alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

provided that both R^5 and R^6 cannot be hydrogen, OH, or SH and when R^5 is OH, R^1, R^2, R^3, R^4, R^7 and R^8 cannot be all hydrogen;

provided that when R^5 or R^6 is phenyl, only one of R^1 or R^2 is H;

provided that when q = 1 and R^x is styryl, anilido, or anilinocarbonyl, only one of R^5 or R^6 is alkyl;

provided that when n is 1, R^1, R^3, R^7, and R^8 are hydrogen, R^2 is hydrogen, alkyl or aryl, R^4 is unsubstituted amino or amino substituted with one or more alkyl or aryl radicals, and R^5 is hydrogen, alkyl or aryl, then R^6 is other than hydroxy; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Preferably, R^5 and R^6 can independently be selected from the group consisting of H, aryl, heterocycle, quaternary heterocycle, and quaternary heteroaryl,

wherein said aryl, heteroaryl, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of

alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A-$, $P(OR^{13})OR^{14}$, $S+R^{13}R^{14}A-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A-$, S, SO, SO_2, S^+R^7A-, PR^7, $P(O)R^7$, $P^+R^7R^8A-$, or phenylene,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR^7)OR^8$.

More preferably, R^5 or R^6 has the formula:

$$-Ar-(R^y)_t$$

wherein:

t is an integer from 0 to 5;

Ar is selected from the group consisting of phenyl, thiophenyl, pyridyl, piperazinyl, piperonyl, pyrrolyl, naphthyl, furanyl, anthracenyl, quinolinyl, isoquinolinyl, quinoxalinyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyrimidinyl, thiazolyl, triazolyl, isothiazolyl, indolyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, and benzoisothiazolyl; and

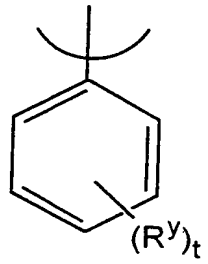
one or more R^y are independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13}, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl,

polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene.

Most preferably, R^5 or R^6 has the formula (II):



(II)

Another embodiment of the invention is further directed to compounds of Formula I wherein at least one or more of the following conditions exist:

(1) R^1 and R^2 are independently selected from the group consisting of hydrogen and alkyl. Preferably, R^1 and R^2 are independently selected from the group consisting of C_{1-6} alkyl. More preferably, R^1 and R^2 are the same C_{1-6} alkyl. Still more preferably, R^1 and R^2 are n-butyl; and/or

(2) R^3 and R^4 are independently selected from the group consisting of hydrogen and OR^9 wherein R^9 is defined as set forth above. Preferably, R^3 is hydrogen and R^4 is OR^9. Still more preferably, R^3 is hydrogen and R^4 is hydroxy; and/or

(3) R^5 is substituted aryl. Preferably, R^5 is substituted phenyl. More preferably, R^5 is phenyl substituted with a radical selected from the group consisting of OR^{13}, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, and

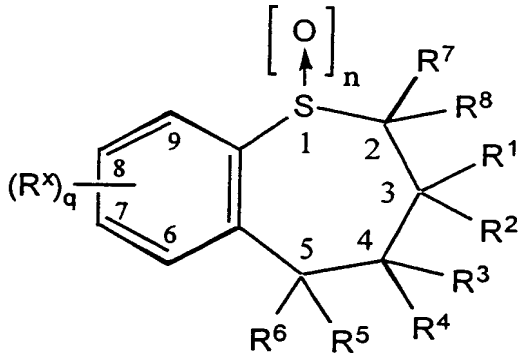
$NR^{13}SO_2NR^{14}R^{15}$ wherein R^{13}, R^{14} and R^{15} are as set forth above. Still more preferably, R^5 is phenyl substituted with OR^{13}. Still more preferably, R^5 is phenyl substituted at the para or meta position with OR^{13} wherein R^{13} comprises a quaternary heterocycle, quaternary heteroaryl or substituted amino; and/or

(4) R^6 is hydrogen; and/or

(5) R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl. Preferably, R^1 and R^2 are independently selected from the group C_{1-6} alkyl. Still more preferably, R^1 and R^2 are hydrogen; and/or

(6) R^x is selected from the group consisting of OR^{13} and $NR^{13}R^{14}$. Preferably, R^x is selected from the group consisting of alkoxy, amino, alkylamino and dialkylamino. Still more preferably, R^x is selected from the group consisting of methoxy and dimethylamino.

Another embodiment of the invention is further directed to compounds of formula 1:



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wherein:

q is an integer from 1 to 4;

n is an integer from 0 to 2;

R^1 and R^2 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl,

dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl,

wherein alkyl, alkenyl, alkynyl, haloalkyl, alkylaryl, arylalkyl, alkoxy, alkoxyalkyl, dialkylamino, alkylthio, (polyalkyl)aryl, and cycloalkyl optionally are substituted with one or more substituents selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{10}R^wA^-$, SR^9, $S^+R^9R^{10}A^-$. $P^+R^9R^{10}R^{11}A^-$, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$,

wherein alkyl, alkenyl, alkynyl, alkylaryl, alkoxy, alkoxyalkyl, (polyalkyl)aryl, and cycloalkyl optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A-$, S, SO, SO_2, $S^+R^9A^-$, $P^+R^9R^{10}A^-$, or phenylene,

wherein R^9, R^{10}, and R^W are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, acyl, heterocycle, ammoniumalkyl, arylalkyl, carboxyalkyl, carboxyheteroaryl, carboxyheterocycle, carboalkoxyalkyl, carboxyalkylamino, heteroarylalkyl, heterocyclylalkyl, and alkylammoniumalkyl; or

R^1 and R^2 taken together with the carbon to which they are attached form C_3-C_{10} cycloalkyl;

R^3 and R^4 are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, acyloxy, aryl, heterocycle, OR^9, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9, wherein R^9 and R^{10} are as defined above; or

R^3 and R^4 together form =O, $=NOR^{11}$, =S, $=NNR^{11}R^{12}$, $=NR^9$, or $=CR^{11}R^{12}$,

wherein R^{11} and R^{12} are independently selected

from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, arylalkyl, alkenylalkyl, alkynylalkyl, heterocycle, carboxyalkyl, carboalkoxyalkyl, cycloalkyl, cyanoalkyl, OR^9, NR^9R^{10}, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, CO_2R^9, CN, halogen, oxo, and $CONR^9R^{10}$, wherein R^9 and R^{10} are as defined above, provided that both R^3 and R^4 cannot be OH, NH_2, and SH, or

R^{11} and R^{12} together with the nitrogen or carbon atom to which they are attached form a cyclic ring;

R^5 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, OR^9, SR^9, $S(O)R^9$, SO_2R^9, and SO_3R^9,

wherein alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, quaternary heterocycle, and quaternary heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, $C(O)OM$, COR^{13}, $NR^{13}C(O)R^{14}$, $NR^{13}C(O)NR^{14}R^{15}$, $NR^{13}CO_2R^{14}$, $OC(O)R^{13}$, $OC(O)NR^{13}R^{14}$, $NR^{13}SOR^{14}$, $NR^{13}SO_2R^{14}$, $NR^{13}SONR^{14}R^{15}$, $NR^{13}SO_2NR^{14}R^{15}$, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

wherein:

A^- is a pharmaceutically acceptable anion and M is

a pharmaceutically acceptable cation,

said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7, NR^7R^8, SR^7, $S(O)R^7$, SO_2R^7, SO_3R^7, CO_2R^7, CN, oxo, $CONR^7R^8$, $N^+R^7R^8R^9A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7R^8$, $P^+R^7R^8R^9A^-$, and $P(O)(OR^7)OR^8$, and

wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7, $N^+R^7R^8A^-$, S, SO, SO_2, $S^+R^7A^-$, PR^7, $P(O)R^7$, $P^+R^7R^8A^-$, or phenylene, and R^{13}, R^{14}, and R^{15} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, arylalkyl, alkylarylalkyl, alkylheteroarylalkyl, alkylheterocyclylalkyl, cycloalkyl, heterocycle, heteroaryl, quaternary heterocycle, quaternary heteroaryl, heterocyclylalkyl, heteroarylalkyl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, alkylammoniumalkyl, and carboxyalkylaminocarbonylalkyl,

wherein alkyl, alkenyl, alkynyl, arylalkyl, heterocycle, and polyalkyl optionally have one or more carbons replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, $S^+R^9A^-$, PR^9, $P^+R^9R^{10}A^-$, $P(O)R^9$, phenylene, carbohydrate, amino acid, peptide, or polypeptide, and

R^{13}, R^{14}, and R^{15} are optionally substituted with one or more groups selected from the group consisting

of hydroxy, amino, sulfo, carboxy, alkyl, carboxyalkyl, heterocycle, heteroaryl, sulfoalkyl, quaternary heterocycle, quaternary heteroaryl, quaternary heterocyclylalkyl, quaternary heteroarylalkyl, guanidinyl, OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{10}R^{11}A-$, $S^+R^9R^{10}A-$, and $C(O)OM$,

wherein R^{16} and R^{17} are independently selected from the substituents constituting R^9 and M; or

R^{13} and R^{14}, together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocycle that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy and quaternary salts; or

R^{14} and R^{15}, together with the nitrogen atom to which they are attached, form a cyclic ring; and

R^6 is hydroxy; and

R^7 and R^8 are independently selected from the group consisting of hydrogen and alkyl; and

one or more R^x are independently selected from the group consisting of H, alkyl, alkenyl, alkynyl, polyalkyl, acyloxy, aryl, arylalkyl, halogen, haloalkyl, cycloalkyl, heterocycle, heteroaryl, polyether, quaternary heterocycle, quaternary heteroaryl, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, $S(O)_2R^{13}$, SO_3R^{13}, $S^+R^{13}R^{14}A-$, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)NR^{13}R^{14}$, $NR^{14}C(O)R^{13}$, $C(O)OM$, COR^{13}, OR^{18}, $S(O)_nNR^{18}$, $NR^{13}R^{18}$,

$NR^{18}OR^{14}$, $N^+R^9R^{11}R^{12}A^-$, $P^+R^9R^{11}R^{12}A^-$, amino acid, peptide, polypeptide, and carbohydrate,

wherein alkyl, alkenyl, alkynyl, cycloalkyl, aryl, polyalkyl, heterocycle, acyloxy, arylalkyl, haloalkyl, polyether, quaternary heterocycle, and quaternary heteroaryl can be further substituted with OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, $P^+R^9R^{11}R^{12}A^-$, $S^+R^9R^{10}A^-$, or C(O)OM, and

wherein R^{18} is selected from the group consisting of acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl,

wherein acyl, arylalkoxycarbonyl, arylalkyl, heterocycle, heteroaryl, alkyl, quaternary heterocycle, and quaternary heteroaryl optionally are substituted with one or more substituents selected from the group consisting of OR^9, NR^9R^{10}, $N^+R^9R^{11}R^{12}A^-$, SR^9, $S(O)R^9$, SO_2R^9, SO_3R^9, oxo, CO_2R^9, CN, halogen, $CONR^9R^{10}$, SO_3R^9, SO_2OM, $SO_2NR^9R^{10}$, $PO(OR^{16})OR^{17}$, and C(O)OM,

wherein in R^x, one or more carbons are optionally replaced by O, NR^{13}, $N^+R^{13}R^{14}A-$, S, SO, SO_2, $S^+R^{13}A^-$, PR^{13}, $P(O)R^{13}$, $P^+R^{13}R^{14}A-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl,

wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9, $N^+R^9R^{10}A^-$, S, SO, SO_2, S^+R^9A-, PR^9, $P^+R^9R^{10}A-$, or $P(O)R^9$;

wherein quaternary heterocycle and quaternary heteroaryl are optionally substituted with one or more

groups selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R^{15}A^-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$,

provided that both R^5 and R^6 cannot be hydrogen, OH, or SH;

provided that when R^5 is phenyl, only one of R^1 or R^2 is H; or

a pharmaceutically acceptable salt, solvate, or prodrug thereof.

The invention is further directed to a compound selected from among:

$$R^{20} - R^{19} - R^{21} \qquad \text{(Formula DI)}$$

$$\begin{array}{c} R^{22} \\ | \\ R^{20} - R^{19} - R^{21} \end{array} \qquad \text{(Formula DII)},$$

and

$$\begin{array}{c} R^{22} \\ | \\ R^{20} - R^{19} - R^{21} \\ | \end{array} \qquad \text{(Formula DIII)}$$

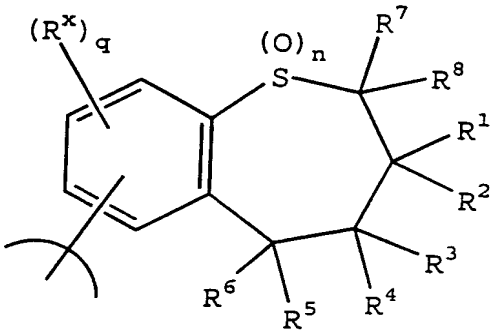
R^{23}

wherein R^{19} is selected from the group consisting of alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide, wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can optionally have one or more carbon atoms replaced by O, NR^7, $N^+R^7R^8$, S, SO, SO_2, $S^+R^7R^8$, PR^7, $P^+R^7R^8$, phenylene, heterocycle, quatarnary heterocycle, quaternary heteroaryl, or aryl,

wherein alkane diyl, alkene diyl, alkyne diyl, polyalkane diyl, alkoxy diyl, polyether diyl, polyalkoxy diyl, carbohydrate, amino acid, peptide, and polypeptide can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13}, $NR^{13}R^{14}$, SR^{13}, $S(O)R^{13}$, SO_2R^{13}, SO_3R^{13}, $NR^{13}OR^{14}$, $NR^{13}NR^{14}R^{15}$, NO_2, CO_2R^{13}, CN, OM, SO_2OM, $SO_2NR^{13}R^{14}$, $C(O)NR^{13}R^{14}$, C(O)OM, COR^{13}, $P(O)R^{13}R^{14}$, $P^+R^{13}R^{14}R15A-$, $P(OR^{13})OR^{14}$, $S^+R^{13}R^{14}A^-$, and $N^+R^9R^{11}R^{12}A^-$;

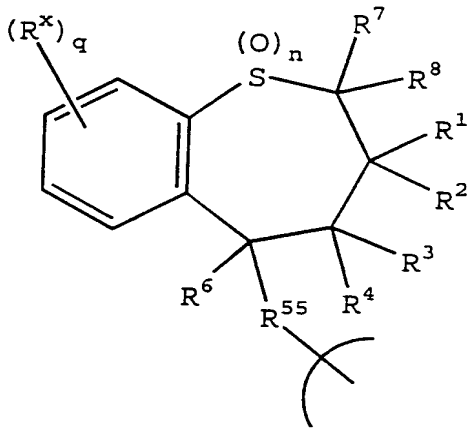
wherein R^{19} further comprises functional linkages by which R^{19} is bonded to R^{20}, R^{21}, or R^{22} in the compounds of Formulae DII and DIII, and R^{23} in the compounds of Formula DIII. Each of R^{20}, R^{21}, or R^{22} and R^{23} comprises a benzothiepine moiety as described above that is therapeutically effective in inhibiting ileal bile acid transport.

The invention is also directed to a compound selected from among Formula DI, Formula DII and Formula DIII in which each of R^{20}, R^{21}, R^{22} and R^{23} comprises a benzothiepine moiety corresponding to the Formula:



(Formula DIV)

or:

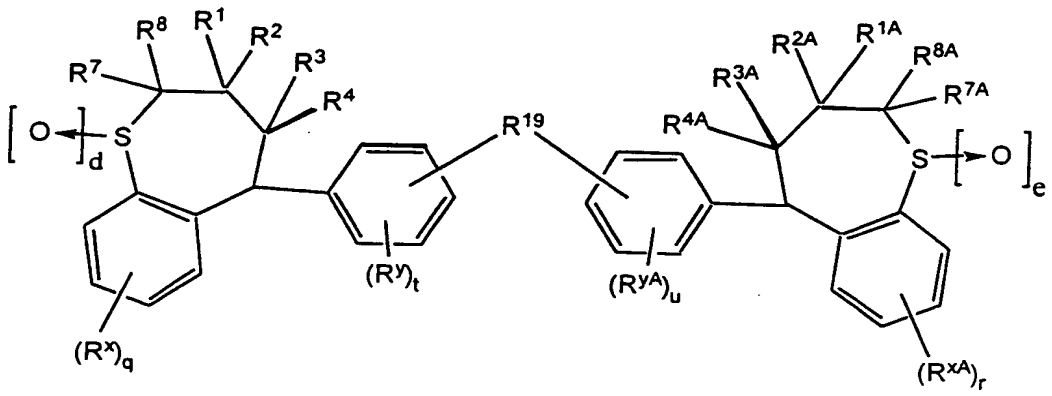


(Formula DIVA)

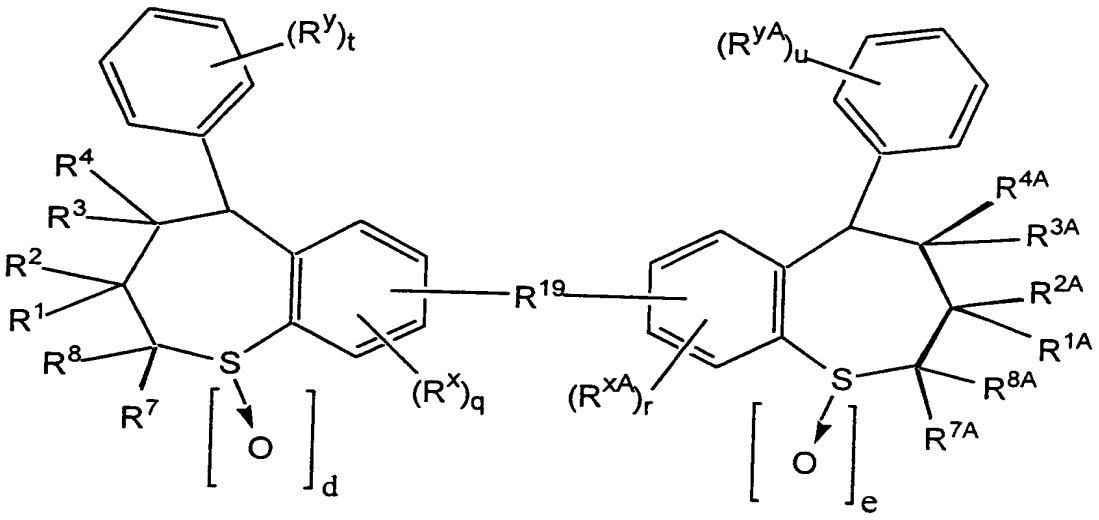
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^x, q, and n are as defined in Formula I as described above, and R^{55} is either a covalent bond or arylene.

In compounds of Formula DIV, it is particularly preferred that each of R^{20}, R^{21}, and R^{22} in Formulae DII and DIII, and R^{23} in Formula DIII, be bonded at its 7- or 8-position to R^{19}. In compounds of Formula DIVA, it is particularly preferred that R^{55} comprise a phenylene moiety bonded at a *m*- or *p*-carbon thereof to R^{19}.

Examples of Formula DI include:



(III)



(IV)

and